MEDICAL EDUCATION RESOURCE

Biological Oxidation and Electron Transport Chain

? BIOLOGICAL OXIDATION & ELECTRON TRANSPORT CHAIN (ETC)

(Including: Primary/Secondary/Tertiary Metabolism, Redox Potential, Biological Oxidation, Oxidases, Cytochrome Oxidase)

? PRIMARY, SECONDARY & TERTIARY METABOLISM

? Primary Metabolism

Metabolic pathways essential for **survival and growth** of cells.
Includes:

- Glycolysis
- TCA cycle
- Oxidative phosphorylation
- Fatty acid oxidation
- Amino acid metabolism

Purpose: Energy production + synthesis of basic cellular components.

? Secondary Metabolism

Metabolic pathways that produce **specialized compounds** not essential for basic survival but important for adaptation.

Examples:

- Porphyrins
- Melanin
- Ketone bodies
- Neurotransmitters
- Hormones

Purpose: Specialized physiologic functions.

? Tertiary Metabolism (Detoxification / Protective Metabolism)

Pathways that deal with **xenobiotics, drugs, toxins, reactive metabolites**.

Includes:

- Cytochrome P450 system
- Phase I detoxification (oxidation, reduction, hydrolysis)
- Phase II detoxification (conjugation)
- Antioxidant systems (GSH, catalase, SOD)

? REDOX POTENTIAL (E?')

? Definition

Redox potential is the tendency of a substance to:

- **Accept electrons (get reduced)** ? high positive E?
- **Donate electrons (get oxidized)** ? negative E?

Electrons flow **from lower to higher redox potential** in the ETC.

? Clinical relevance

- Used to arrange ETC components in order
- Explains **unidirectional electron flow**
- Helps understand poisoning (e.g., cyanide blocks cytochrome oxidase)

? BIOLOGICAL OXIDATION

? Definition

enzyme-mediated transfer of electrons from donors ? acceptors, producing energy.

? Main types of biological oxidation

1. Dehydrogenation

Removal of hydrogen atoms:

- Enzymes: **Dehydrogenases**
- Coenzymes: **NAD?, NADP?, FAD, FMN**

2. Oxidation via Molecular Oxygen

Two major pathways:

A. Oxidases

- Use **O? as electron acceptor**
- Do NOT incorporate oxygen into substrate
- Produce **H?O? or H?O**

Examples:

- Cytochrome oxidase
- Xanthine oxidase
- Monoamine oxidase (MAO)

B. Oxygenases

- Incorporate oxygen into substrate
- Types:
    - **Monooxygenases** (mixed-function oxidases)
        - One atom ? substrate

        - One atom ? water

    - **Dioxygenases**

        - Both O atoms into substrate

? OXIDASES (High-Yield List)

? Cytochrome oxidase (Complex IV)

Terminal enzyme of ETC ? reduces O? ? H?O.

? Xanthine oxidase

Purine degradation ? xanthine ? uric acid.

? Monoamine oxidase

Degradation of neurotransmitters (dopamine, serotonin, noradrenaline).

? L-Amino acid oxidase

Oxidizes L-amino acids ? ?-ketoacids + H?O?.

? D-Amino acid oxidase

Oxidizes D-amino acids (peroxisomes).

? Glucose oxidase

Glucose ? gluconic acid + H?O?.

? CYTOCHROME OXIDASE (COMPLEX IV)

? Function

- Final enzyme of ETC
- Accepts electrons from **cytochrome c**
- Reduces molecular oxygen to **water**

? Components

- Cytochromes **a** and **a?**
- Contains **copper (Cu²?)** centers

? Significance

- Responsible for **majority of ATP production**
- Maintains proton gradient for ATP synthase

? Inhibitors (VERY HIGH YIELD)

- **Cyanide**
- **Carbon monoxide (CO)**
- **Hydrogen sulfide (H?S)**

- **Azide**

These inhibit Complex IV ? stop electron flow ? **cellular hypoxia** despite normal oxygen (histotoxic hypoxia).

? TYPES OF ELECTRON CARRIERS IN ETC

1. **Flavoproteins** (FMN, FAD)
2. **Iron–sulfur proteins**
3. **Ubiquinone (CoQ)**
4. **Cytochromes (b, c?, c, a, a?)**
5. **Copper centers** (in Complex IV)

Electron flow always proceeds from:
More negative ? more positive redox potential

? OVERVIEW OF ETC COMPLEXES

? Complex I — NADH dehydrogenase

- NADH ? CoQ
- Pumps protons
- Contains FMN and Fe-S

? Complex II — Succinate dehydrogenase

- FADH? ? CoQ
- Does NOT pump protons

? CoQ (Ubiquinone)

- Mobile carrier between complexes I/II ? III
- Accepts electrons + protons

? Complex III — Cytochrome bc?

- Transfers electrons to cytochrome c
- Fe-S + cytochromes b/c?

? Cytochrome c

- Mobile, water-soluble carrier
- Transfers electrons to Complex IV

? Complex IV — Cytochrome oxidase

- Transfers electrons to O? ? H?O
- Pumps protons

? Complex V — ATP synthase

- Uses proton gradient ? synthesizes ATP

- 3 ATP per NADH; 2 ATP per FADH? (classic values)

? CLINICAL NOTES

- **Cyanide poisoning:** inhibits Complex IV ? rapid cellular asphyxia
- **CO poisoning:** binds cytochrome oxidase + hemoglobin
- **Dinitrophenol (DNP):** uncoupler ? dissipates proton gradient ? heat production
- **Barbiturates/Rotenone:** inhibit Complex I
- **Antimycin A:** inhibits Complex III
- **Oligomycin:** inhibits ATP synthase (Complex V)

? ULTRA-SHORT EXAM REVISION

- ETC occurs in **inner mitochondrial membrane**.
- Electrons flow from **NADH/FADH? ? O?** based on **redox potential**.
- **Complex IV = Cytochrome oxidase**, inhibited by cyanide/CO.
- Oxidases use O? as electron acceptor; may form H?O?.
- Primary metabolism = essential pathways; secondary = specialized; tertiary = detoxification.
- ATP synthesis requires intact **proton gradient**.

- CoQ and cytochrome c are **mobile carriers**.

? DEHYDROGENASES

? Definition

Enzymes that **remove hydrogen atoms** (2H: 2e? + 2H?) from substrates and pass electrons to coenzymes like **NAD?** or **FAD**.

? Features

- Key in **biological oxidation**
- Present in glycolysis, TCA cycle, ?-oxidation, amino acid metabolism
- Usually located in **mitochondria** (except cytosolic dehydrogenases like LDH)

? Important Examples

- **Lactate dehydrogenase (LDH)**: Lactate ? pyruvate
- **Malate dehydrogenase**: Malate ? OAA (NADH)
- **Isocitrate dehydrogenase**: Rate-limiting in TCA
- **Glucose-6-phosphate dehydrogenase (G6PD)**: Generates NADPH
- **Alcohol dehydrogenase**: Alcohol ? acetaldehyde

- **Succinate dehydrogenase**: Succinate ? fumarate (FADH?)

? NAD? (Nicotinamide Adenine Dinucleotide)

? Role

- Mobile electron carrier
- Accepts **2 electrons + 1 proton** ? NADH
- Participates mainly in **catabolic**, energy-producing pathways

? Where NAD? is used

- Glycolysis (G3P-DH)
- PDH complex
- TCA cycle
- ?-oxidation
- Ethanol metabolism
- Lactate ? pyruvate

? NADH yields energy via ETC

1 NADH ? **3 ATP** (classic) or **2.5 ATP** (modern value)

? FAD (Flavin Adenine Dinucleotide)

? Role

- Accepts **2 electrons + 2 protons** ? FADH?
- Bound tightly to enzymes (prosthetic group)

? Where FAD is used

- **Succinate dehydrogenase** (Complex II)
- **Acyl-CoA dehydrogenase** (first step of ?-oxidation)
- PDH/?-KGDH complexes (via FAD-dependent E3 unit)

? Energy yield

1 FADH? ? **2 ATP** (classic) or **1.5 ATP** (modern)

? CYTOCHROMES

? Definition

Electron-carrying proteins with **heme iron** that cycles between:

- Fe^{2}? (reduced)

- Fe^{3}? (oxidized)

? Location

- **Electron Transport Chain** (ETC)

? Types (High-Yield)

- **Cytochrome b** (Complex III)
- **Cytochrome c?** (Complex III)
- **Cytochrome c** (mobile carrier)
- **Cytochrome a / a?** (Complex IV)

? Function

Carry **single electrons**; arranged by **redox potential** from lower ? higher.

? OXYGENASES

? Definition

Enzymes that incorporate molecular oxygen into substrates.

? Types

? 1. Monooxygenases (Mixed-Function Oxidases)

- Insert **one atom** of O? into substrate
- Other atom ? H?O
- Require **NADPH + cytochrome P450**
- Role: Drug metabolism, steroid synthesis

Examples:
Cytochrome P450 enzymes, tryptophan hydroxylase

? 2. Dioxygenases

- Insert **both oxygen atoms** into substrate

Examples:

- Prolyl hydroxylase
- Tyrosine hydroxylase
- Tryptophan pyrrolase

? HIGH-ENERGY COMPOUNDS

? Definition

Molecules releasing large amounts of free energy (?G° highly negative) upon hydrolysis.

? High-Energy Compounds (VERY HIGH YIELD)

1. ATP (adenosine triphosphate)

- Universal energy currency
- ?G° ? –7.3 kcal/mol

2. Phosphoenolpyruvate (PEP)

- Highest high-energy phosphate: –14.8 kcal/mol

3. 1,3-Bisphosphoglycerate (1,3-BPG)

4. Creatine phosphate

- Energy reservoir in muscle
- Used for rapid ATP regeneration

5. Succinyl-CoA

- High-energy thioester bond
- Generates **GTP** in TCA cycle

6. Acetyl-CoA

- High-energy thioester used in multiple pathways

7. Carbamoyl phosphate

- High-energy substrate of urea cycle/pyrimidine synthesis

8. UDP-glucose

- High-energy sugar for glycogen synthesis

? ORGANIZATION OF THE ELECTRON TRANSPORT CHAIN (ETC)

ETC is arranged in the **inner mitochondrial membrane** in four large complexes + two mobile carriers.

? Complex I — NADH dehydrogenase

- NADH ? FMN ? Fe-S ? CoQ
- Pumps protons (H?)

? Complex II — Succinate dehydrogenase

- FADH? ? Fe-S ? CoQ
- Does NOT pump protons

? Coenzyme Q (Ubiquinone)

- Mobile lipid-soluble carrier
- Collects electrons from Complex I & II

- Delivers to Complex III

? Complex III — Cytochrome bc?

- Fe-S + cytochromes b & c?
- Transfers electrons to **cytochrome c**
- Pumps protons

? Cytochrome c

- Small, water-soluble mobile protein
- Transfers electrons to Complex IV

? Complex IV — Cytochrome oxidase

- Cytochromes a & a? + copper centers
- Reduces O? ? H?O
- Pumps protons
- Inhibited by: **cyanide, CO, azide, H?S**

? Complex V — ATP Synthase

- Uses proton gradient (proton motive force) to make ATP
- Rotational motor (F?) + catalytic head (F?)

? DIRECTION OF ELECTRON FLOW

Electrons always flow from:
NADH ? FMN ? Fe-S ? CoQ ? Cyt b ? Cyt c? ? Cyt c ? Cyt a ? Cyt a? ? O?

Because **redox potential increases stepwise**.

? PROTON PUMPING SUMMARY

COMPLEX	PROTON PUMPING	ENERGY YIELD
I	Yes	NADH ? ETC
II	No	FADH? ? ETC
III	Yes	Contributes to PMF
IV	Yes	Final step to oxygen

Complex V is NOT a pump—it **uses** the gradient.

? NADH SHUTTLES (Why they are needed)

? Problem

- **Cytosolic NADH cannot cross the inner mitochondrial membrane**.
- Yet NADH from glycolysis must transfer its electrons into the mitochondria for ATP production.

? Solution

Two biochemical shuttles carry **reducing equivalents**, not NADH itself:

1. **Malate–Aspartate shuttle** (high-efficiency, produces 3 ATP/NADH classic, 2.5 modern)
2. **Glycerol-3-phosphate shuttle** (lower efficiency, produces 2 ATP/NADH classic, 1.5 modern)

? MALATE–ASPARTATE SHUTTLE (HIGH YIELD)

Location: Liver, heart, kidney
Efficiency: Highest (yields full NADH ATP)

? Steps of the Malate–Aspartate Shuttle

1. Cytosolic NADH reduces oxaloacetate ? malate

- Enzyme: **Malate dehydrogenase (cytosolic)**
- Malate carries electrons across membrane.

2. Malate enters mitochondria via malate–?-ketoglutarate transporter.

3. Inside mitochondria: Malate ? oxaloacetate

- Enzyme: **Mitochondrial malate dehydrogenase**
- NAD? ? **NADH** formed inside mitochondria (**full ATP yield**).

4. Oxaloacetate ? Aspartate

- Enzyme: **Aspartate transaminase (AST)**

5. Aspartate exits mitochondria via glutamate–aspartate transporter.

6. Aspartate ? Oxaloacetate (in cytosol)

- Shuttle completes.

> **? Energy Yield**

Each cytosolic NADH ? **equivalent mitochondrial NADH**
? generates **3 ATP (classic)** or **~2.5 ATP (modern)**.

? GLYCEROL-3-PHOSPHATE SHUTTLE (For comparison)

(Not asked often but needed for contrast)

- Found in **brain & skeletal muscle**.
- Cytosolic NADH converts DHAP ? glycerol-3-phosphate.
- Mitochondrial FAD is reduced ? FADH? ? **Complex II**
- Produces **less ATP** because electrons enter ETC later.

? FLOW OF ELECTRONS IN ETC (VERY HIGH-YIELD)

Electrons move from **low ? high redox potential**, finally reducing **O? ? H?O**.

? Flow from NADH

NADH ? Complex I (FMN, Fe-S) ? CoQ ? Complex III (cyt b, c?) ?
Cytochrome c ? Complex IV (cyt a, a? + Cu²?) ? **O?**

? Flow from FADH?

FADH? (Complex II) ? Fe-S ? CoQ ? Complex III ? Complex IV ? **O?**

(No proton pump at Complex II ? lower ATP yield)

? Proton Pumping Sites

- **Complex I**
- **Complex III**
- **Complex IV**

Complex II does NOT pump protons.

? OXIDATIVE PHOSPHORYLATION (ATP production)

? Concept

Couples:

- **Electron transport** through ETC
  with

- **ATP synthesis** by ATP synthase (Complex V)

Done via **chemiosmotic mechanism**.

? CHEMIOSMOTIC THEORY (Mitchell’s theory)

Electron flow ? pumps protons into intermembrane space ?
creates **proton motive force** (PMF) consisting of:

- Electrical gradient (??)

- Chemical gradient (?pH)

Protons return via **ATP synthase**, generating ATP.

? ATP SYNTHASE (Complex V)

? Structure:

- **F?:** Membrane channel that allows proton entry

- **F?:** Catalytic unit that synthesizes ATP

? Mechanism:

Three sites rotate between:

- Loose (bind ADP + Pi)

- Tight (form ATP)
- Open (release ATP)

This rotation is driven by proton flow.

? ENERGY YIELD (Classic vs Modern)

MOLECULE	CLASSIC ATP YIELD	MODERN P/O RATIO
NADH	3 ATP	~2.5 ATP
FADH?	2 ATP	~1.5 ATP

? INHIBITORS OF OXIDATIVE PHOSPHORYLATION

? Complex I inhibitors

- Rotenone
- Barbiturates
- Piericidin A

? Complex II inhibitor

- Malonate

? Complex III inhibitor

- Antimycin A

? Complex IV inhibitors

- Cyanide
- Carbon monoxide
- Azide
- H?S

? ATP synthase inhibitor

- Oligomycin

? Uncouplers (destroy proton gradient ? no ATP)

- DNP
- Thermogenin (brown fat)
- High-dose aspirin

? KEY CLINICAL PEARLS

- Cyanide ? immediate inhibition of Complex IV ? **cellular hypoxia**.
- DNP ? collapses proton gradient ? **hyperthermia**.
- Oligomycin ? Stops ATP synthesis, **electron flow also stops**.
- Aspartate aminotransferase is essential for malate shuttle.

- Glycerol-3-phosphate shuttle is active during **brain activity & fasting**.

? CHEMIOSMOTIC THEORY (MITCHELL'S THEORY)

? Core Concept

Electron transport through the ETC pumps **protons (H?)** from the mitochondrial matrix ? intermembrane space.

This creates a **proton motive force (PMF)** made of:

- **Electrochemical gradient** (charge difference)
- **pH gradient** (H? concentration difference)

ATP synthase uses this **proton gradient** to synthesize ATP.

This coupling of:

- **Oxidation (ETC)**
  with
- **Phosphorylation (ATP formation)**

is called **oxidative phosphorylation**.

? Key Features of Chemiosmotic Theory

- ETC complexes I, III, IV act as **proton pumps**.

- Inner mitochondrial membrane is **impermeable to H?**.
- Proton return through **ATP synthase (Complex V)** drives ATP formation.
- Proton flow causes a **rotational** change in ATP synthase ? mechanical ? chemical energy conversion.
- Any disruption of gradient = ATP synthesis stops.

? ATP SYNTHASE (COMPLEX V)

Mitochondrial enzyme that converts **proton flow ? ATP**.

? Structure

F? Unit (membrane embedded)

- Forms the **proton channel**.
- Rotation of F? drives movement of catalytic sites.

F? Unit (projects into matrix)

- Catalyzes: **ADP + Pi ? ATP**
- Has 3 catalytic ?-subunits.

? Mechanism (Binding Change Model)

Each ?-subunit cycles through:

1. **Loose state** ? binds ADP + Pi
2. **Tight state** ? synthesizes ATP
3. **Open state** ? releases ATP

Rotational catalysis is driven by **H? moving through F?**.

? INHIBITORS OF ATP SYNTHESIS (MEMBRANE ATP SYNTHASE BLOCKERS)

? Oligomycin

- Blocks **F? proton channel**.
- Prevents proton entry ? ATP synthesis stops.
- Electron transport ALSO stops because gradient becomes too high.

? Atractyloside

- Inhibits **ADP/ATP translocase** (ANT transporter).
- Prevents entry of ADP ? ATP synthesis halts.

? Venturicidin & Dicyclohexylcarbodiimide (DCCD)

- Bind F? subunit ? block proton flow.

? Key Clinical Concept

Inhibiting ATP synthase **blocks both phosphorylation AND electron transport**.

? UNCOUPLERS OF OXIDATIVE PHOSPHORYLATION

Uncouplers **allow protons to leak back** into matrix **WITHOUT passing through ATP synthase**.

Result:

- **No ATP formation**
- **Electron transport continues at full speed**
- Energy released as **heat**

? Major Uncouplers (High Yield)

? 1. 2,4-Dinitrophenol (DNP)

- Lipid-soluble proton carrier
- Causes hyperthermia
- Previously used as a weight-loss drug (dangerous)

? 2. Thermogenin (UCP-1)

- Natural uncoupler in **brown adipose tissue**
- Generates **non-shivering thermogenesis** in infants

? 3. High-dose salicylates (aspirin overdose)

- Cause hyperventilation + metabolic acidosis
- Increase heat production

? 4. FCCP (Carbonyl cyanide p-trifluoromethoxyphenylhydrazone)

- Lab uncoupler
- Strong protonophore

? Effects of Uncouplers

- ETC speeds up
- Oxygen consumption increases
- ATP production ?
- Heat ?
- NADH/FADH? oxidized faster

? IONOPHORES (VERY HIGH YIELD)

Ionophores are compounds that **transport ions across membranes**, collapsing gradients.

Used widely in research; some seen in poisoning.

? Types of Ionophores

? 1. Valinomycin

- **Potassium ion (K?) carrier**
- Inserts into membranes ? collapses K? gradient
- Example of **mobile carrier ionophore**

? 2. Nigericin

- Exchanges **K? for H?**
- Affects proton gradient ? indirectly uncouples ATP synthesis

? 3. Gramicidin

- Forms **ion channels** in membranes
- Allows Na?, K? to move freely ? disrupts membrane potential

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? Difference Between Ionophores & Uncouplers

FEATURE	UNCOUPLERS	IONOPHORES
Primary action	Dissipate H? gradient	Move ions (H?, K?, Na?)
Effect on ETC	ETC continues fast	ETC may slow or collapse depending on ion
Effect on ATP	ATP synthesis ?	ATP synthesis ?

FEATURE	UNCOUPLERS	IONOPHORES
Example	DNP, thermogenin	Valinomycin, nigericin

? ULTRA-HIGH YIELD 1-MIN REVISION

- Chemiosmotic theory links **electron flow ? proton gradient ? ATP synthesis**.
- ATP synthase has **F? channel + F? catalytic head**.
- **Oligomycin** blocks ATP synthase (F?).
- **DNP** uncouples ETC from ATP formation; heat ?.
- **Thermogenin** physiologic uncoupler in brown fat.
- **Ionophores** move ions across membranes (valinomycin = K? carrier).
- Proton gradient is essential for ATP generation.

? IMPORTANT POINTS TO REMEMBER — BIOLOGICAL OXIDATION

? Chemiosmotic Theory

- ETC pumps **H? ions** from mitochondrial matrix ? intermembrane space.
- Creates **proton motive force (PMF)**: electrical + chemical gradient.

- Proton gradient drives **ATP synthase**.
- Inner mitochondrial membrane is **impermeable to H?**.
- Any substance that collapses H? gradient **stops ATP synthesis**.
- Proton pumping occurs only at **Complex I, III, IV**.

? ATP Synthase (Complex V)

- Composed of **F? (proton channel)** + **F? (ATP-forming head)**.
- Works by **rotational catalysis** (binding change mechanism).
- ?-subunits go through **Loose ? Tight ? Open** states.
- Uses energy of proton flow to convert **ADP + Pi ? ATP**.
- Blocked by **oligomycin** (F? inhibitor).
- Most ATP of the cell comes from **oxidative phosphorylation**, not substrate-level phosphorylation.

? Inhibitors of ATP Synthesis

- **Oligomycin** blocks F? ? no H? flow ? no ATP.
- **Atractyloside** inhibits **ADP/ATP translocase** (ANT).
- **Venturicidin, DCCD** directly block proton channel.

- Inhibition of ATP synthase also **stops ETC** due to back-pressure of proton gradient.

? Uncouplers of Oxidative Phosphorylation

- Allow H? to leak back into matrix **without** passing through ATP synthase.
- Oxidation continues, ATP formation stops, heat increases.
- **DNP**: toxic drug uncoupler ? hyperthermia.
- **Thermogenin (UCP-1)**: physiologic uncoupler in **brown fat** ? heat generation in infants.
- **Aspirin overdose** acts as an uncoupler ? metabolic acidosis + fever.
- Uncouplers ? ATP, ? O? consumption, ? heat.

? Ionophores

- Lipid-soluble molecules that move ions across membranes.
- Collapse electrochemical gradients ? inhibit ATP synthesis.
- **Valinomycin** ? carries K? across membrane.
- **Nigericin** ? exchanges H? with K? ? affects proton gradient.
- **Gramicidin** ? forms ion channels for Na?/K?.
- Ionophores differ from uncouplers:
    - Uncouplers move **H?** only;

- Ionophores move other ions too (K?, Na?, etc.), collapsing membrane potential.

? Electron Transport Chain Overview

- Electrons flow **from low ? high redox potential**.
- Order: NADH ? Complex I ? CoQ ? Complex III ? Cyt c ? Complex IV ? O?.
- Complex II (succinate dehydrogenase) does NOT pump protons.
- Oxygen is the **final electron acceptor** ? forms water.
- CoQ (ubiquinone) & cytochrome c are **mobile electron carriers**.

? Energy Yield

- NADH ? 3 ATP (classic), ~2.5 ATP (modern).
- FADH? ? 2 ATP (classic), ~1.5 ATP (modern).
- ATP synthesis requires **intact proton gradient**.

? High-Yield Clinical Facts

- **Cyanide, CO, H?S** inhibit **cytochrome oxidase (Complex IV)** ? cellular hypoxia.
- **Rotenone/Barbiturates** inhibit **Complex I**.
- **Antimycin A** inhibits **Complex III**.

- **Oligomycin** blocks ATP synthase (F?).
- **DNP** uncouples ? dangerous hyperthermia.
- Brown fat activity (thermogenin) helps **heat production** in newborns.

? CLINICAL CASE–BASED QUESTIONS — BIOLOGICAL OXIDATION & ETC

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1. Cyanide Poisoning After Burning Plastic

A 28-year-old man is brought unconscious after inhaling fumes from burning plastic. He has severe lactic acidosis and normal oxygen saturation.

Diagnosis:

Acute **cyanide poisoning**.

Biochemical Basis:

- Cyanide inhibits **Complex IV (cytochrome oxidase)**.
- ETC stops ? no proton gradient ? no ATP.
- Cells shift to **anaerobic glycolysis** ? lactic acidosis.

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2. Infant with Severe Hypothermia but Normal Glucose

A newborn cannot maintain body temperature despite warm environment. Brown fat biopsy shows absence of **UCP-1**.

Diagnosis:

Defective **thermogenin (UCP-1)**.

Biochemical Basis:

- UCP-1 is a **physiologic uncoupler**.
- No heat production ? impaired non-shivering thermogenesis.

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3. Athlete Using Weight-Loss Pills Develops Hyperthermia

After taking “fat-burning pills,” an athlete develops high fever, tachycardia, and acidosis. The pills contain **DNP (dinitrophenol)**.

Diagnosis:

DNP-induced uncoupling.

Biochemical Basis:

- DNP carries H? across membrane ? no ATP synthesis.
- ETC runs uncontrollably ? heat production ??.
- Patient develops **hyperthermia**.

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4. Elderly Man with Acute Liver Failure

A patient with liver failure shows accumulation of NADH in mitochondria and inability to regenerate NAD?.

Diagnosis:

Failure of **Malate–Aspartate Shuttle**.

Explanation:

- Without shuttle, cytosolic NADH from glycolysis cannot enter mitochondria.
- ATP production falls sharply ? lactic acidosis develops.

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5. Patient with Oligomycin Ingestion

A farmer ingests a pesticide containing **oligomycin**. He develops muscle weakness and metabolic crisis.

Diagnosis:

Inhibition of **ATP synthase (Complex V)**.

Biochemical Basis:

- Oligomycin blocks **F? proton channel**.
- Stops proton flow ? no ATP synthesis.
- ETC also stops because proton gradient becomes too steep.

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6. Aspirin Overdose in a Child

A 5-year-old boy ingests high-dose aspirin. He has fever, hyperventilation, and metabolic acidosis.

Diagnosis:

Salicylate-induced uncoupling of oxidative phosphorylation.

Mechanism:

- High-dose aspirin acts as a weak uncoupler.
- ETC continues but ATP drops ? heat ? ? respiratory alkalosis followed by acidosis.

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7. Patient with Hypoxia but Normal Oxygen Levels

A factory worker exposed to CO collapses. His PaO? is normal but tissues are hypoxic.

Diagnosis:

Carbon monoxide poisoning

Biochemical Basis:

- CO binds **cytochrome oxidase** and **hemoglobin**.
- ETC blockade ? ATP stops ? cellular hypoxia.

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8. Bodybuilder with Muscle Pain After Intense Exercise

Biopsy shows swollen mitochondria and collapsed membrane potential due to a compound that increased K? permeability.

Diagnosis:

Poisoning by **valinomycin** (ionophore).

Mechanism:

- Carries **K?** across membrane ? collapses electric gradient.
- ATP synthesis impaired due to loss of membrane potential.

9. Farmer with Rotenone Exposure

A farmer exposed to insecticide presents with weakness and lactic acidosis.

Diagnosis:

Complex I inhibition by rotenone.

Biochemical Basis:

- NADH cannot transfer electrons to ETC.
- NAD? unavailable for glycolysis ? lactate ?.

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10. Young Woman with Mitochondrial Myopathy

Muscle biopsy shows normal Complex I–IV but defective **ADP/ATP translocase (ANT)**.

Diagnosis:

Atractyloside-type inhibition.

Mechanism:

- ADP cannot enter mitochondria ? ATP cannot be formed.
- ATP remains trapped inside matrix; cytosol suffers deficiency.

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11. Sepsis Patient with High Oxygen Use but Low ATP

A critically ill patient with sepsis has very high O? consumption yet low ATP levels.

Diagnosis:

Uncoupling due to mitochondrial damage.

Explanation:

- ETC works rapidly but proton gradient is lost.
- ATP synthase cannot function ? ATP drops.

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12. Person with Severe Muscle Fatigue After FCCP Exposure

Lab worker exposed to FCCP complains of heat intolerance and muscle fatigue.

Diagnosis:

Exposure to a **potent synthetic uncoupler**.

Mechanism:

- FCCP transports protons directly ? collapses gradient.
- ATP production stops ? heat ?.

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13. Child with Lactic Acidosis After Intense Exercise

Biochemistry shows large buildup of pyruvate and lactate but normal oxygen.

Diagnosis:

Failure of **glycerol-3-phosphate shuttle** (less efficient NADH transfer).

Mechanism:

- Cytosolic NADH cannot be oxidized.
- Converts pyruvate ? lactate.

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14. Man with Mitochondrial Ion Channel-Forming Antibiotic Poisoning

After consuming an antibiotic-contaminated food, a man presents with massive cellular swelling.

Diagnosis:

Gramicidin poisoning

Mechanism:

- Gramicidin forms **membrane ion channels** ? Na?/K? freely diffuse.
- Membrane potential collapses ? ATP production stops.

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15. Neonate with Hyperthermia and Failure to Gain Weight

Brown adipose biopsy shows excessive UCP-1 activity.

Diagnosis:

Overactive thermogenin (UCP-1).

Mechanism:

- Excessive uncoupling ? extreme heat production.
- Energy lost as heat ? weight loss.

? MCQs — Biological Oxidation & ETC

1. Which complex pumps protons into the intermembrane space?

A. Complex II
B. Complex V
C. **Complex III**
D. ADP/ATP translocase

Answer: C

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2. Which component is the final electron acceptor in ETC?

A. Cytochrome c
B. Coenzyme Q
C. **Oxygen**
D. NAD?

Answer: C

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3. The chemiosmotic theory states that ATP synthesis is driven by:

A. Substrate-level phosphorylation
B. High-energy intermediates
C. **Proton gradient across inner mitochondrial membrane**
D. Electron carriers directly phosphorylating ADP

Answer: C

---

4. Which enzyme is inhibited by oligomycin?

A. Complex I
B. Complex III
C. **ATP synthase (Complex V)**
D. Coenzyme Q oxidoreductase

Answer: C

---

5. In the malate–aspartate shuttle, cytosolic NADH is converted into:

A. FADH?
B. DHAP
C. **Mitochondrial NADH**
D. ATP directly

Answer: C

---

6. Dinitrophenol (DNP) causes:

A. Inhibition of Complex I
B. Increase in ATP
C. Decrease in oxygen consumption
D. **Uncoupling of oxidative phosphorylation**

Answer: D

---

7. Thermogenin (UCP-1) is found in:

A. Liver
B. Kidney
C. **Brown adipose tissue**
D. Heart

Answer: C

---

8. Which shuttle yields the highest ATP per NADH?

A. Glycerol-3-phosphate shuttle
B. **Malate–aspartate shuttle**
C. Carnitine shuttle
D. Citrate shuttle

Answer: B

---

9. Which is a mobile electron carrier in the ETC?

A. Cytochrome b
B. Complex II
C. **Cytochrome c**
D. Complex IV

Answer: C

---

10. Rotenone inhibits which ETC complex?

A. Complex II
B. Complex III
C. **Complex I**
D. Complex IV

Answer: C

---

11. Which inhibitor blocks ADP from entering mitochondria?

A. Oligomycin
B. DNP
C. **Atractyloside**
D. FCCP

Answer: C

---

12. A patient with cyanide poisoning will have inhibition of:

A. Complex I
B. Complex II
C. Complex III
D. **Complex IV**

Answer: D

---

13. Which process continues during uncoupling?

A. ATP synthesis

B. Proton pumping by Complex V

C. **Electron transport**

D. Maintenance of membrane potential

Answer: C

---

14. The F? subunit of ATP synthase functions as:

A. NADH oxidase

B. Rotating catalytic head

C. **Proton channel**

D. Antiporter

Answer: C

---

15. The primary ion transported by valinomycin is:

A. H?

B. Na?

C. Ca^{2}?

D. **K?**

Answer: D

---

16. Which shuttle operates in the brain and skeletal muscle?

A. Carnitine shuttle

B. Malate-aspartate shuttle

C. **Glycerol-3-phosphate shuttle**

D. Citrate shuttle

Answer: C

---

17. Cyanide causes what biochemical change?

A. Increased ATP

B. **Cellular hypoxia with normal PaO?**

C. Increased NADH

D. Increased oxidative phosphorylation

Answer: B

---

18. Which complex does NOT pump protons?

A. Complex I

B. Complex III

C. Complex IV

D. **Complex II**

Answer: D

---

19. What drives ATP synthesis mechanically?

A. NADH

B. FADH?

C. **Rotation of ATP synthase (F?–F?)**

D. Cytochrome c

Answer: C

---

20. Glycerol-3-phosphate shuttle transfers electrons to:

A. NAD?

B. **FAD (Complex II)**

C. Cytochrome c

D. FMN

Answer: B

---

21. Ionophores disrupt oxidative phosphorylation by:

A. Blocking ATP synthase

B. Blocking electron transport

C. **Collapsing ion gradients**

D. Inhibiting CoQ

Answer: C

---

22. Uncouplers increase:

A. ATP

B. NADH

C. **Heat production**

D. Proton gradient

Answer: C

---

23. The proton-motive force consists of:

A. Na?/K? gradient

B. FAD/FADH? ratio

C. **?pH + ?electrical gradient**

D. ATP/ADP ratio

Answer: C

---

24. Which complex contains cytochromes a & a??

A. Complex I

B. Complex II

C. Complex III

D. **Complex IV**

Answer: D

---

25. The main physiological uncoupler is:

A. Valinomycin

B. **Thermogenin (UCP-1)**

C. Atractyloside

D. Oligomycin

Answer: B

? VIVA VOCE — Biological Oxidation & ETC

---

1. What is the chemiosmotic theory?

Electron transport pumps protons to create a **proton gradient**, and ATP is synthesized when protons flow back through **ATP synthase**.

---

2. Where does the proton gradient form?

Across the **inner mitochondrial membrane**.

---

3. Which complexes pump protons?

Complex I, III, and IV.

---

4. Which ETC complex does NOT pump protons?

Complex II (Succinate dehydrogenase).

---

5. What is proton motive force (PMF)?

The combination of **electrical** and **chemical (pH)** gradient across the inner membrane.

---

6. What is the role of ATP synthase?

Uses PMF to convert **ADP + Pi ? ATP**.

---

7. What are the two components of ATP synthase?

F? (proton channel) and **F? (catalytic head).**

---

8. What happens in the F? unit?

Protons enter and **drive rotation** of the enzyme.

---

9. What happens in the F? unit?

ATP is **synthesized** by the ?-subunits.

---

10. Name the three states of ?-subunits during ATP synthesis.

Loose ? Tight ? Open.

---

11. What inhibits ATP synthase?

Oligomycin.

---

12. What does oligomycin block?

The **F? proton channel**, stopping proton entry.

---

13. What are uncouplers?

Compounds that **allow protons to leak back** into the matrix without ATP synthesis.

---

14. Give two examples of uncouplers.

DNP, **thermogenin (UCP-1)**.

---

15. What is the physiological uncoupler?

Thermogenin in brown fat.

---

16. What is the effect of uncouplers on ATP synthesis?

ATP falls, **heat production increases**, **ETC speeds up**.

---

17. What are ionophores?

Lipid-soluble molecules that **transport ions across membranes**, collapsing gradients.

---

18. Example of a K? ionophore?

Valinomycin.

---

19. Example of an ion-channel–forming antibiotic?

Gramicidin.

---

20. What does nigericin transport?

Exchanges **H? for K?**.

---

21. What is the final electron acceptor in ETC?

Oxygen, reduced to **water**.

---

22. Which ETC complex contains cytochromes a and a??

Complex IV (Cytochrome oxidase).

---

23. Which complex contains FMN?

Complex I.

---

24. Which complex receives electrons from FADH??

Complex II.

---

25. What is the order of electron flow from NADH?

NADH ? Complex I ? CoQ ? Complex III ? Cyt c ? Complex IV ? **O?**.

---

26. What is the redox potential?

Tendency of a molecule to **accept electrons** (positive = strong oxidant).

---

27. What carries electrons between Complex III and IV?

Cytochrome c.

---

28. What carries electrons between Complex I/II and III?

Coenzyme Q (Ubiquinone).

---

29. What shuttle transfers cytosolic NADH to mitochondria with full ATP yield?

Malate–aspartate shuttle.

---

30. What shuttle is used in brain and muscle?

Glycerol-3-phosphate shuttle.

---

31. What does the glycerol-3-phosphate shuttle regenerate?

FADH?.

---

32. Which shuttle yields less ATP?

Glycerol-3-phosphate shuttle.

---

33. What is atractyloside?

Inhibitor of **ADP/ATP translocase (ANT)**.

---

34. What is the effect of cyanide on ETC?

Inhibits **Complex IV**, stopping electron flow.

---

35. What is the effect of antimycin A?

Inhibits **Complex III**.

---

36. What is the effect of rotenone?

Inhibits **Complex I**.

---

37. What happens to NADH during oxidative phosphorylation?

It is **oxidized to NAD?** and donates electrons to ETC.

---

38. What forms when oxygen accepts electrons?

Water.

---

39. What is the P/O ratio of NADH?

~**2.5 ATP** (modern value).

---

40. What happens to ETC when ATP synthase is blocked?

ETC **stops** because the proton gradient becomes too steep.